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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/175,683	10/20/1998	LI HOW CHEN	10275-134001	7184

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/175,683	Applicant(s) CHEN ET AL.	
	Examiner Richard Schnizer, Ph. D	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *6-8,10,20,31-37 and 48-76* is/are pending in the application.

4a) Of the above claim(s) *49,56,63 and 70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *6-8,10,20,31-37,48,50-55,57-62,64-69 and 71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *20 October 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/03 has been entered.

A request for suspension was received with the request for continued examination. The period of suspension has ended, and prosecution now resumes.

Claims 49-76 were added as requested.

Claims 6-8, 10, 20, 31-37, and 48-76 are pending.

Newly submitted claims 49, 56, 63, and 70 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims are directed to polypeptides. The originally claimed invention is directed to a method of producing a polypeptide, so the inventions are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the protein can be isolated from its natural source, e.g. plasmodium falciparum. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claim 49, 56, 63, and 70 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 6-8, 10, 20, 31-37, 48, 50-55, 57-62, 64-69, and 71-76 are under consideration in this Office Action.

Compliance with 37 CFR 1.121

Applicant is reminded that 37 CFR 1.121 sets forth the format for amendments to the claims. Failure to comply with 37 CFR 1.121 can result in issuance of a notice of non-responsive amendment. The instant claims were filed in accordance with the format for practice prior to July 2003. In the interests of compact prosecution the Examiner has directed their entry.

Claim Objections

Claim 6 is objected to because it recites the word "of" rather than the word "or" in the phrase "parasite protein of fragment thereof" in the first line of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8, 10, 20, 31-37, 48, 50-55, 57-62, 64-69, and 71-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8, 10, 31-37, 48, 50-55, 57-62, 64-69, 71-76 and recite "the milk of a nonhuman transgenic animal" without antecedent basis. Deletion of "the" is suggested.

Claims 6, 8, and 50-55 are confusing because it is unclear what is and is not a modified nucleic acid sequence. In particular, the phrase "wherein said modified nucleic acid sequence has been modified by replacing on or more AT-containing codons of said modified nucleic acid sequence as it naturally occurs in a parasite" is confusing. In this phrase, the second instance of "said modified nucleic acid sequence" renders the claim indefinite. In view of the teachings of the specification, the nucleic acid as it occurs in the parasite does not exist in a modified state but a natural AT-rich state. However, the claims explicitly require that the nucleic acid as it occurs in the parasite is in a modified state, i.e. "said modified nucleic acid sequence as it naturally occurs in a parasite". As such it is not clear what is intended by the phrase "said modified nucleic acid sequence".

These claims are also indefinite because they recite "the same amino acid as a replaced codon as derived from said parasite" without antecedent basis. Further, it is unclear what is intended by "a replaced codon as derived from said parasite". As the Examiner understands the invention, replaced codons are not derived from a parasite, but from a set of preferred mammalian codons.

Claims 7, 8, 10, 20, 31-48, and 64-76 are indefinite because they recite recites "the coding sequence as it naturally occurs in a parasite" without antecedent basis. These claims also recite "encoding the same amino acid as the replaced portion of said AUUUA mRNA instability motif" without proper antecedent basis. In particular "the

same amino acid" is recited without antecedent basis. In cases where the replaced codon overlaps, but is not contained within, an AUUUA motif, only one or two bases in an AUUUA motif will be replaced. In these cases, "the replaced portion of said AUUUA mRNA instability motif" will not encode an amino acid because it will consist of only one or two bases.

Claim 20 recites "the coding sequence as it naturally occurs in a parasite" without antecedent basis.

Claim 32 is indefinite because it recites "each of said AUUUA mRNA instability motifs" without antecedent basis. Claim 10, from which claim 32 depends, provides an antecedent for only a single AUUUA motif.

Claims 73-76 are indefinite because they recite "[t]he method of claim 20" without antecedent basis. Claim 20 is not directed to a method, it is directed to a composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 53, 60, 67, and 74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 27.

Claim 34 is amended to be drawn to the genus of nucleic acids in which all of the codons of a naturally occurring nucleic acid sequence encoding a parasite protein are replaced with a codon or codons preferred by a mammalian cell for purposes of expressing that protein. As such the claim embraces nucleic acids encoding parasite proteins that comprise only one type of amino acid, i.e. those proteins in which all of the codons are replaced with a single type of codon preferred by a mammalian cell. The claim also embraces nucleic acids encoding parasite proteins that do not comprise, in the natural state, any codon which is the most preferred for expression in a mammal. That is, nucleic acids in which each and every codon is not the most preferred for mammalian expression, and for which a more preferable codon may be substituted.

The instant specification fails to describe a single parasite protein that consists of only a single amino acid, and fails to describe a single nucleic acid encoding a parasite protein wherein the nucleic acid lacks any of the codons that are most preferred for expression in mammalian cells. For example, the specification discloses a naturally occurring nucleic acid encoding a Plasmodium falciparum antigen SEQ ID NO:2. This nucleic acid contains codons encoding N9 (AAC), E16 (GAG), K49 (AAG), F62 (TTC), F98 (TTC), and S100 (AGC). Each of these codons is the most preferred codon for its respective amino acid for expression in human cells according to instant Fig. 3b. So, it would be impossible to substitute the most preferred codon for each of the codons in SEQ ID NO:2. The specification fails to teach any example of a nucleic acid encoding a parasite protein for which this would be possible. As such, claim 34 as amended introduces new matter.

New claims 53, 60, 67, and 74 are drawn to the promoters from the "alpha-ovalbumin" and "bovine lactoglobulin" gene. The specification as filed provides no written support for such promoters, and so these claims introduce new matter. The Medline database was searched for "alpha-ovalbumin", and a total of five hits was obtained. All five hits pertained to fusion proteins between ovalbumin and an alpha subunit of another protein. As such, there appears to be no such thing as an alpha-albumin gene or promoter. When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not new matter is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. See MPEP 2163.06.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 8, 50, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), Rosen et al (US Patent U5,304,489, issued 4/19/1994), and either one of Seed (1998), or Milland et al (US Patent 6,130,062, issued 10/10/00,

Dziegiel teaches an expression vector comprising a nucleic acid encoding an antigen of *Plasmodium falciparum.* See abstract. The expression vector may be used in mammalian cells for the purpose of producing and isolating the antigen, and may be used to construct transgenic animals for the purpose of producing the antigen. The polypeptide produced may be used as a vaccine. See column 18, lines 54-65, and column 19, lines 61-63. The nucleic acid may be modified by silent mutations which favor the codon usage of the organism in which the nucleic acid will be expressed. See column 20, line 66 to column 21, line 7; and column 21, lines 36-40. The nucleic acid encoding the antigen is only 30% G+C, and comprises at least two AUUUA motifs within the coding region. See column 16, lines 40-43, and bases 962-966, and 1896-1900 in the sequence bridging columns 13 and 14.

Dziegiel does not teach expressing the antigen in the milk of the transgenic animal, or reducing the AT-content of the antigen-encoding nucleic acid.

Rosen teaches methods of producing recombinant proteins in the milk of transgenic mammals. The method comprises operatively linking a milk-specific promoter to an exogenous gene sequence and generating a transgenic animal comprising the hybrid gene. Rosen teaches the use of a variety of milk-specific promoters including promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. The expressed protein is secreted into the mammal's milk, from which it can be purified. See abstract. The transgenic animals may comprise the construct in their germ line cells. See paragraph 19 of Brief Summary. Rosen teaches that expression in mammalian

mammary tissue solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and should be less expensive. See e.g. paragraph 10 of the Brief Summary.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2, lines 7-11. Preferred codons are always those with the highest possible GC-content. See lines 33-37, and Table 1, bridging columns 7 and 8.

Milland teaches methods of increasing production in mammalian cells of proteins encoded by nucleic acids with AT rich regions in their exons, wherein the method comprises altering the nucleic acid by reducing or lowering the amount of A and/or T in said region and transfecting a host cell with said nucleic acid. See brief summary paragraph 11 and detailed description paragraph 14. Milland teaches that reducing A+T content may improve stability of transcripts, increase delivery of mRNA to the cytoplasm, increase efficiency of translation by ribosomes, and increase translation due to mRNA superstructure or in fact a combination of two or more of these factors. See detailed description paragraph 19.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the codon usage of the transgene of Dziegiel, because both Dziegiel and Seed teach that one should optimize the codons of a heterologous gene according to the organism in which it is to be expressed, and because Seed teaches that codon optimization can improve expression of foreign genes in mammalian cells. One would have been motivated to decrease the AT-content of the transgene because

it is apparent from the teachings of Seed that the most preferred codons in mammalian systems are the most GC-rich codons, or because Milland teaches that doing so may increase the production of the protein in eukaryotic cells. One would have been motivated to produce the parasite protein in the milk of the transgenic animal because Rosen teaches that this solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and is less expensive. See e.g. paragraph 10 of the Brief Summary.

Thus the invention as a whole was prima facie obvious.

Claims 7, 8, 57, and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), in view of Rosen et al (US Patent U5,304,489, issued 4/19/1994), Seed (1998), Akashi (1994).

Dziegiel teaches an expression vector comprising a nucleic acid encoding an antigen of *Plasmodium falciparum*. See abstract. The expression vector may be used in mammalian cells for the purpose of producing and isolating the antigen, and may be used to construct transgenic animals for the purpose of producing the antigen. The polypeptide produced may be used as a vaccine. See column 18, lines 54-65, and column 19, lines 61-63. The nucleic acid may be modified by silent mutations which favor the codon usage of the organism in which the nucleic acid will be expressed. See column 20, line 66 to column 21, line 7; and column 21, lines 36-40. The nucleic acid encoding the antigen is only 30% G+C, and comprises at least two AUUUA motifs within

the coding region. See column 16, lines 40-43, and bases 962-966, and 1896-1900 in the sequence bridging columns 13 and 14.

Dziegiel does not teach expressing the antigen in the milk of the transgenic animal, or the removal of AUUUA mRNA instability motifs.

Rosen teaches methods of producing recombinant proteins in the milk of transgenic mammals. The method comprises operatively linking a milk-specific promoter to an exogenous gene sequence and generating a transgenic animal comprising the hybrid gene. Rosen teaches the use of a variety of promoters including promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. The expressed protein is secreted into the mammal's milk, from which it can be purified. See abstract. The transgenic animals may comprise the construct in their germ line cells. See paragraph 19 of Brief Summary. Rosen teaches that expression in mammalian mammary tissue solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and should be less expensive. See e.g. paragraph 10 of the Brief Summary.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2, lines 7-11. Preferred codons are always those with the highest possible GC-content. See lines 33-37, and Table 1, bridging columns 7 and 8. Seed also teaches avoiding the use of AUUUA motifs in synthetic genes. See column 12, lines 35-37.

Akashi teaches that the function of AUUUA motifs is not restricted to their location within the mRNA. These motifs need not be located in the 3'-untranslated region of mRNAs, and are capable of destabilizing mRNAs even when located in the coding region. See abstract, and Fig. 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the transgene of Dziegiel for expression in mammalian cells as taught by Seed, including by removal of AUUUA motifs. One would have been motivated to do so in order to improve expression of the transgene by improving stability of its mRNA. One would have had a reasonable expectation of improving the stability of the because Akashi teaches that AUUUA sequences in open reading frames can destabilize mRNA. One would have been motivated to produce the parasite protein in the milk of the transgenic animal because Rosen teaches that this solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and is less expensive. See e.g. paragraph 10 of the Brief Summary.

Thus the invention as a whole was prima facie obvious.

Claims 10, 20, 31-37, 48, 64, and 66-68, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), Rosen et al (US Patent U5,304,489, issued 4/19/1994), Seed (1998), Akashi (1994), Milland (2000).

Dziegiel teaches an expression vector comprising a nucleic acid encoding an antigen of *Plasmodium falciparum*. See abstract. The expression vector may be used in mammalian cells for the purpose of producing and isolating the antigen, and may be

used to construct transgenic animals for the purpose of producing the antigen. The polypeptide produced may be used as a vaccine. See column 18, lines 54-65, and column 19, lines 61-63. The nucleic acid may be modified by silent mutations which favor the codon usage of the organism in which the nucleic acid will be expressed. See column 20, line 66 to column 21, line 7; and column 21, lines 36-40. The nucleic acid encoding the antigen is only 30% G+C, and comprises at least two AUUUA motifs within the coding region. See column 16, lines 40-43, and bases 962-966, and 1896-1900 in the sequence bridging columns 13 and 14.

Dziegiel does not teach expressing the antigen in the milk of the transgenic animal, reducing the AT-content of the nucleic acid, or removal of AUUUA mRNA instability motifs.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2, lines 7-11. Preferred codons are always those with the highest possible GC-content. See lines 33-37, and Table 1, bridging columns 7 and 8. Seed also teaches avoiding the use of AUUUA motifs in synthetic genes. See column 12, lines 35-37.

Milland teaches methods of increasing production in mammalian cells of proteins encoded by nucleic acids with AT rich regions in their exons, wherein the method comprises altering the nucleic acid by reducing or lowering the amount of A and/or T in said region and transfecting a host cell with said nucleic acid. See brief summary paragraph 11 and detailed description paragraph 14. Milland teaches that reducing A+T content may improve stability of transcripts, increase delivery of mRNA to the

cytoplasm, increase efficiency of translation by ribosomes, and increase translation due to mRNA superstructure or in fact a combination of two or more of these factors. See detailed description paragraph 19.

Akashi teaches that the function of AUUUA motifs is not restricted to their location within the mRNA. These motifs need not be located in the 3'-untranslated region of mRNAs, and are capable of destabilizing mRNAs even when located in the coding region. See abstract, and Fig. 1.

Rosen teaches methods of producing recombinant proteins in the milk of transgenic mammals. The method comprises operatively linking a milk-specific promoter to an exogenous gene sequence and generating a transgenic animal comprising the hybrid gene. Rosen teaches the use of a variety of promoters including promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. The expressed protein is secreted into the mammal's milk, from which it can be purified. See abstract. The transgenic animals may comprise the construct in their germ line cells. See paragraph 19 of Brief Summary. Rosen teaches that expression in mammalian mammary tissue solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and should be less expensive. See e.g. paragraph 10 of the Brief Summary.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the codon usage of the transgene of Dziegiel as taught by Seed. One would have been motivated to do so because Seed teaches that codon

optimization can improve expression of foreign genes in mammalian cells. One would have been motivated to decrease the AT-content of the transgene because it is apparent from the teachings of Seed that the most preferred codons in mammalian systems are the most GC-rich codons, and because Milland teaches that doing so may increase the production of the protein in eukaryotic cells. Similarly one would have been motivated to remove AUUUA motifs from the transgene because Seed teaches that this should be done. Furthermore, it would be inherent in the process of selecting GC-rich codons. For example, depending on the reading frame, the sequence AUUUA can comprise an AUU codon encoding I, a UUU codon encoding F, or a UUA codon encoding L. The preferred codon for each of these amino acids, as taught by Seed, comprises a G or C. Thus if one followed the teachings of Seed in terms of codon selection, one would necessarily remove AUUUA motifs from the transgene open reading frame. One also would have been motivated to remove AUUUA sequences from the transgene open reading frame because Akashi teaches that AUUUA sequences in open reading frames can destabilize mRNA. One would have been motivated to produce the parasite protein in the milk of the transgenic animal because Rosen teaches that this solves problems associated with the expression of polypeptides in prokaryotic or eukaryotic cell culture, and is less expensive. See e.g. paragraph 10 of the Brief Summary.

Claims 35 and 36 are included in this rejection because, although they require specific yields of protein, the recited method steps are obvious, and the results are considered to be inherent in the absence of evidence that suggests unexpected results.

Thus the invention as a whole was prima facie obvious.

Claims 6 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), in view of Rosen et al (US Patent U5,304,489, issued 4/19/1994), White et al (US Patent 5,856,178, issued 1/5/1999), and either one of Seed (1998), or Milland (2000).

The teachings of Dziegiel (1993), Rosen (1994), Seed (1998), Milland (2000), and are discussed above. These teachings render obvious methods of making a parasite protein in the milk of a transgenic animal, including goats and cows, wherein the animal comprises a nucleic acid encoding the parasite protein wherein the nucleic acid is linked to a milk specific promoter, and has been modified to reduce it's A+T content. These references teach promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. (see Rosen at paragraph 2 of the detailed description.

The references do not teach a bovine lactoglobulin promoter or a caprine casein promoter.

White teaches methods of expressing lytic peptides in the milk of transgenic animals, and provides a list of milk specific promoters at Table 1, columns 5 and 6. This table includes beta casein promoters, bovine lactoglobulin promoters, and caprine casein promoters.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of the milk-specific promoters taught by the combined references

because it was clear to one of ordinary skill that these promoters were art recognized equivalents for the purpose of producing proteins in mammalian milk. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 7 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), in view of Rosen et al (US Patent U5,304,489, issued 4/19/1994), Seed (1998), Akashi (1994), and White et al (US Patent 5,856,178, issued 1/5/1999).

The teachings of Dziegiel (1993), Seed (1998), Akashi (1994), and Rosen (1994) are discussed above. These teachings render obvious methods of making a parasite protein in the milk of a transgenic animal, including goats and cows, wherein the animal comprises a nucleic acid encoding the parasite protein wherein the nucleic acid is linked to a milk specific promoter, and has been modified to remove AUUUA mRNA instability motifs. These references teach promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. (see Rosen at paragraph 2 of the detailed description.

The references do not teach a bovine lactoglobulin promoter or a caprine casein promoter.

White teaches methods of expressing lytic peptides in the milk of transgenic animals, and provides a list of milk specific promoters at Table 1, columns 5 and 6. This table includes beta casein promoters, bovine lactoglobulin promoters, and caprine casein promoters.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of milk-specific promoters taught by the combined references because it was clear to one of ordinary skill that these promoters were art recognized equivalents for the purpose of producing proteins in mammalian milk. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 10 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel (1993), in view of Rosen et al (US Patent U5,304,489, issued 4/19/1994), Seed (1998), Akashi (1994), Milland, and White et al (US Patent 5,856,178, issued 1/5/1999).

The teachings of Dziegiel (1993), Seed (1998), Akashi (1994), Milland and Rosen (1994) are discussed above. These teachings render obvious methods of making a parasite protein in the milk of a transgenic animal, including goats and cows,

wherein the animal comprises a nucleic acid encoding the parasite protein wherein the nucleic acid is linked to a milk specific promoter, and has been modified to reduce its A+T content and to remove AUUUA mRNA instability motifs. These references teach promoters for alpha-casein, beta-casein, gamma-casein, kappa-casein, alpha-lactalbumin, beta-lactoglobulin, and whey acidic protein. (see Rosen at paragraph 2 of the detailed description.

The references do not teach a bovine lactoglobulin promoter or a caprine casein promoter.

White teaches methods of expressing lytic peptides in the milk of transgenic animals, and provides a list of milk specific promoters at Table 1, columns 5 and 6. This table includes beta casein promoters, bovine lactoglobulin promoters, and caprine casein promoters.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of milk-specific promoters taught by the combined references because it was clear to one of ordinary skill that these promoters were art recognized equivalents for the purpose of producing proteins in mammalian milk. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 7/24/03 have been fully considered as they apply to the rejections above but they are not persuasive.

Applicant considers the rejection at pages 17-29 of the response.

At pages 17-20, Applicant argues that Dziegiel is not an appropriate reference and does not fall within the scope of the applicable prior art. Applicant asserts that Dziegiel does not teach:

1) reduction of AT-content of any nucleic acid,

2) removal of AUUUA motifs from any nucleic acid, or the importance of such,

3) alteration of nucleic acids to increase the use of codons preferred or more abundant in mammalian cells,

4) inclusion of any nucleic acid construct in the cells of a transgenic mammal, and

5) recovery of proteins from milk of a transgenic animal.

The PTO notes that assertions 3 and 4 on this list are false. Dziegiel clearly teaches that the nucleic acid may be modified by silent mutations which favor the codon usage of the organism in which the nucleic acid will be expressed (see column 20, line 66 to column 21, line 7; and column 21, lines 36-40), that the nucleic acid may be used in mammalian cells for the purpose of producing and isolating the antigen, and that the nucleic acid may be used to construct transgenic animals for the purpose of producing the antigen. Host animals include e.g., sheep, cattle, goats, and pigs. See column 18, lines 54-68. Regarding item 1, because Dziegiel recognizes that the P. falciparum

genome is only 30% G+C, and because Dziegiel teaches that codons should be optimized for expression in a mammalian system, Dziegiel effectively teaches decreasing the AT content of P. falciparum genes that one wishes to express in mammals, particularly in view of the teachings of Seed who shows that the most preferred codons for expression in mammals are those with the highest G+C content. See lines 33-37, and Table 1, bridging columns 7 and 8. Furthermore, the Office now relies on Milland who teaches that one should decrease the A+T content of AT-rich exons for expression in mammalian cells. With regard to items 2 and 5, it is noted that Dziegiel was not relied upon to teach these limitations, instead these limitations were taught by Seed and Rosen. While none of the cited art specifically addresses the issue of removal of AUUUA instability motifs from parasite protein sequences, Seed's general teaching that it is advisable to avoid such sequences in proteins designed for expression in mammalian cells would clearly be sufficient to one of ordinary skill in the art who wished to follow the advice of Dziegiel and express a plasmodium antigen in a mammalian cell or organism. So, the cited art clearly addresses each of the points that Applicant raises at page 17 and the first two lines of page 18.

At page 18 of the response, Applicant states that at best Dziegiel provides only a P.falciparum nucleic acid sequence for use in and with a variety of well known vectors including prokaryotes and viruses. This is false. As discussed above Dziegiel explicitly suggests that one should express the proteins of the invention in sheep, cattle, goats, and pigs. Clearly one of ordinary skill, given the teachings of Dziegiel, Seed, and Rosen, would be motivated to express a P.falciparum antigen in a mammal, and would

optimize the codons appropriately, and remove AUUUA motifs as possible. Further, one would be motivated to express the protein in the milk of the animal in view of the teachings of Rosen.

Applicant's statement at page 18, lines 6-9 to the effect that the Examiner is treating the expression of a target polypeptide in milk of a transgenic animal as the expression of a target polypeptide in a vector along the lines of E.coli is confusing. The Examiner clearly relied upon Bleck (now Rosen) to teach how to express recombinant proteins in the milk a transgenic animal. Dziegiel suggested that P.falciparum antigens should be expressed in transgenic mammals, and Rosen teaches a cost-effective way to do this by expressing the proteins in the mammal's milk. One of ordinary skill in the art would be aware of these teachings and would be able to combine them with a reasonable expectation of success.

The balance of pages 18-20 is devoted to a discussion of why Dziegiel is not an appropriate reference. In summary, Applicant argues that the claimed invention is directed to features methods and solutions of problems that are alien and non-analogous to the prior art cited by the Examiner. This is unpersuasive because Applicant has failed to address the fact that Dziegiel clearly and explicitly suggests that the proteins of his invention, i.e. P. falciparum antigens, should be expressed in mammals such as cows, goats, sheep, and pigs. The teachings of Rosen, not to mention those of White, provide guidance as to how to accomplish protein expression in such mammals, and provide motivation to provide expression in mammal milk. Both Dziegiel and Seed advise codon optimization, and it is clear that this would lead to a

decrease in A+T content because Seed shows that mammal-preferred codons are the most G+C rich codons, because Dziegiel teaches that P.falciparum genes comprise only 30% G+C, and because Milland teaches that one should reduce AT-content in AT-rich exons to improve expression in mammalian cells. Seed also advises removal of AUUUA motifs. Applicant has failed to point to any limitation that is not taught by the combined references, and has not provided any logic or reasoning as to why these references could not be combined by one of ordinary skill in the art with a reasonable expectation of success.

At pages 20-22, Applicant argues that even if Dziegiel is analogous art, Dziegiel teaches away from the instant invention. This argument appears to be based on the position that Dziegiel focuses on the use of prokaryotic and viral expression systems and does not provide sufficient guidance to one of ordinary skill to achieve expression in the milk of a transgenic animal. Applicant is reminded that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). In any event, as noted above, Dziegiel provides the suggestion to express codon optimized P.falciparum antigens in mammals, so Dziegiel cannot be considered to teach away from the invention.

At page 22, first paragraph, Applicant argues that Dziegiel does not teach how to arrive at the claimed invention *successfully*, within the constraints of the technically possible. This is unpersuasive because Applicant has failed to consider the contributions of the other cited references as set forth in the rejection, and because

Applicant has presented no evidence or logic to indicate that one of ordinary skill in the art would not have been motivated to combine the cited teachings in the manner suggested, and could not have done so with a reasonable expectation of success.

At page 23, Applicant relies on the abstracts Graves (1998) and Graves (2003) to establish a long felt need in the art for the claimed invention. Applicant did not discuss what specifically in each reference supported the existence of a long felt need. It is noted that the references are directed to prevention of malaria, so any evidence of long felt need would be applicable only to claims that are limited to production of malarial antigens. In any event, Graves (1998) teaches that a malarial vaccine of higher efficacy would be desirable. Applicant has provided no evidence that the instant invention provides a vaccine of higher efficacy than the vaccine of Graves. That is, Applicant has provided no evidence that the invention meets the long felt need of a more efficacious vaccine.

At pages 24-29 Applicant argues that the Examiner has failed to make a prima facie case of obviousness. Applicant first notes that Dziegiel fails to teach all of the elements of the invention and then considers the supporting references. First Applicant considers Bosch. The Office notes that Bosch was dropped from the instant rejection because Bosch taught removal of mRNA instability motifs and codon optimization, and thus was redundant because Seed teaches both of these limitations. Applicant then argues that Seed fails to discuss transgenic mammal systems particularly with regard to gene expression in milk. The PTO notes that Seed was not relied upon to teach these limitations. Seed was relied upon to teach how best to express proteins in mammalian

cells, e.g. by optimizing codons and avoiding AUUUA motifs. Dziegiel suggested expressing P.falciparum antigens in heterologous systems such as mammals, and optimizing codons according to the system used. Rosen provided the motivation and expertise required to express recombinant proteins in mammalian milk.

Next Applicant considers Akashi. Akashi was relied upon to provide evidence that one of skill in the art would now that an AUUUA sequence could be destabilizing regardless of where it existed in an mRNA, thus one of ordinary skill aware of the teachings of Seed and Akashi would avoid inclusion of AUUUA sequences anywhere within a sequence to be transcribed from a modified gene. For these reasons, Applicant's arguments that Akashi fails to teach changing the A+T content of genes, or to consider the problems of expressing parasite proteins in milk are unpersuasive. Because Akashi teaches that AUUUA motifs are destabilizing, one of ordinary skill in the art would be aware that AUUUA motifs in parasite proteins could be destabilizing as well , and would be motivated to remove them for mammalian expression.

Applicant argues that Bleck is silent with regard to codon optimization, reduction of A+T content, and removal of AUUUA motifs. Note that the Bleck reference has been replaced by the Rosen reference, because Rosen teaches more of the claimed promoters than does Bleck. This argument is unpersuasive because neither Bleck nor Rosen was relied upon to teach these limitations as they were taught by Dziegiel, Milland, and/or Seed. Applicant appears to argue that Bleck fails to enable the instant invention because Bleck provides no guidance as to non-lactation controlled proteins and exemplifies only expression of a milk protein in a transgenic mammal. This

argument is unpersuasive to the extent that it may apply to the Rosen reference because Applicant has failed to present any evidence to suggest that non-milk proteins are inherently any more difficult to express in milk than are milk proteins. Neither has Applicant shown that, given the teachings of the prior art regarding codon optimization and removal of AUUUA motifs, one of ordinary skill in the art could not express non-milk proteins in milk with a reasonable expectation of success. Although the following reference was not relied upon in the rejection, it is noted that Meade et al (US Patent 4,873,316, issued 10/10/89) taught that a variety of non-milk proteins, including cell surface proteins, could be expressed in mammal milk. See e.g. abstract, claims, and paragraphs 7-10 of the detailed description. Applicant has not presented any reason or evidence to suggest that a nucleic acid encoding a parasite protein, and modified as suggested by the cited references, could not be expressed in mammalian milk with a reasonable expectation of success.

At page 28, and throughout the response, Applicant argues that the cited references do not suggest combination of their respective teachings. Applicant is reminded that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit

teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). In this case, it is clear that Dziegiel explicitly suggests that one should express P.falciparum proteins in mammals such as sheep, cattle, goats, and pigs, and that Dziegiel suggests that codons should be optimized according to the expression system chosen. Seed provides specific guidance for the optimization of sequences for expression in mammalian cells, including avoidance of AUUUA sequences and codon optimization for resulting in decreased A+T content. Rosen provides the expertise and motivation for expressing the proteins in the milk of the mammals as suggested by Dziegiel. Applicant has failed to show why these references would not be combined in this fashion by one of ordinary skill in the art. As such the rejections are deemed proper.

Conclusion

No claim is allowed.

Claims 51, 55, 58, 62, 65, 69, and 71-76 are free of the art of record. Claims 71-76 are free of the art due to indefiniteness, i.e. they are drawn to the method of claim 20, but claim 20 is a composition not a method. Should these claims be amended to be drawn to the composition of claim 20, claims 71 and 73-75 would be obvious over the art cited in this Action, and claims 72 and 76 would be free of the art of record. Claims drawn to methods of making plasmodium falciparum MSP-1 are considered to be free of the art for the following reasons. While one of skill in the art would be motivated to combine the teachings of the art, to arrive at a transgenic animal comprising a modified P.falciparum MSP-1 transgene, and a method of making the protein, Applicant has demonstrated that, in the absence of the gene modification taught in the specification, no expression of MSP-1 was obtained in the milk of a transgenic mouse. Whereas improvement in gene expression should be expected as a result of gene optimization, the demonstration of MSP-1 expression, where previously there was none, is deemed to be an unexpected result. Applicant is encouraged to limit the claims to methods of expressing MSP-1.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax

number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.